Randomized, Double-Blind, Phase II Trial Comparing Gemcitabine-Cisplatin plus the LTB4 Antagonist LY293111 versus Gemcitabine-Cisplatin plus Placebo in First-Line Non–Small-Cell Lung Cancer

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Introduction: In this phase II study, patients with stage IIIB/IV non–small-cell lung cancer were randomly assigned (1:1:1) to receive LY293111 (200 mg twice daily [200 LY293111] or 600 mg twice daily [600 LY293111]) or placebo for 7 days, followed by concurrent cisplatin (75 mg/m2; day 1) and gemcitabine (1250 mg/m2; days 1 and 8), every 21 days.The primary endpoint was progression-free survival, (PFS), with 75% power to detect 33% improvement compared with placebo (5 months).

Methods: Of 200 randomized patients, 195 were treated. Demographics were well balanced across treatment arms: 65% of the patients were men; median age was 62 years; 85% had stage IV disease; and patients had an Eastern Cooperative Oncology Group performance status of 0 (36%) or 1 (64%).

Results: The most frequent study drug–related toxicities were nausea, vomiting, and fatigue. Response rates were similar across treatment arms (200 LY293111: 20%; 600 LY293111: 25%; placebo: 31%).

Conclusions: Median PFS (95% confidence interval) was not significantly different across treatment arms (200 LY293111: 4.6 months [3.2–5.0]; 600 LY293111: 5.6 months [4.1–6.8]; placebo: 6.0 months [5.2–7.5]). LY293111 combined with gemcitabine-cisplatin did not increase median PFS compared with placebo plus gemcitabine-cisplatin in patients with non–small-cell lung cancer.

Key Words: Cisplatin, Gemcitabine, Chemotherapy, Leukotriene receptor agonist, Lung cancer, LY293111, Peroxisome proliferators, Activated receptor γ agonist.

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LY293111 is a biphenyl-substituted diaryl ether carboxylic acid that functions as a leukotriene B4 (LTB4) receptor antagonist.[1,2] Inhibition of this pathway has been postulated as a target in the treatment of cancer.[3,4] LY293111 also seems to affect the expression of various eicosanoids and is a peroxisome proliferator–activated receptor γ (PPAR-γ) agonist, which is also a potential target for cancer cell inhibition.[5] Chang and Szabo[6] have demonstrated that PPAR-γ protein is expressed in 50% of primary non–small-cell lung cancer (NSCLC). When they treated NSCLC cell lines that expressed PPAR-γ (at both the mRNA and protein level) with known PPAR-γ ligands, it induced terminal differentiation and apoptosis. Adipophilin and adiponectin are two secreted lipid-associated factors that have demonstrated regulation by PPAR-γ agonists.[7,8]

LY293111 has been studied as a single agent and in combination with cytotoxic chemotherapy agents, including gemcitabine.[9–11] In a phase I study, oral LY293111 was generally well tolerated, with a recommended phase II dose of 600 mg orally twice daily.[11] An additional phase I study of LY293111 in combination with gemcitabine, given at 1000 mg/m^2 for 3 of 4 weeks, showed the regimen was well tolerated and established the maximum tolerated dose of LY293111 as 600 mg orally twice daily.[10]

We designed and conducted a phase II, randomized, double-blind trial comparing the combination of gemcitabine plus cisplatin and LY293111 versus the combination of gemcitabine plus cisplatin and placebo in advanced NSCLC.

MATERIALS AND METHODS

Eligible patients (≥18 years of age) had stage IIIB or IV NSCLC, at least one unidimensionally measurable lesion

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meeting Response Evaluation Criteria in Solid Tumors 1.0,[12] an Eastern Cooperative Oncology Group performance status of 1 or less, and adequate organ function. Patients receiving prior chemotherapy or biological therapy for NSCLC were excluded from the study. Patients were randomly assigned to receive LY293111 200 mg twice daily (200 LY293111), LY293111 600 mg twice-daily (600 LY293111), or placebo, followed by gemcitabine (1250 mg/m^2; days 1 and 8), and cisplatin (75 mg/m^2, day 1), every 21 days. Patients received a lead-in treatment (cycle 1) of single-agent oral 200 mg twice-daily LY293111, 600 mg twice-daily LY293111, or placebo for 7 days to achieve steady-state pharmacokinetics. After the lead-in treatment, patients received up to six treatment cycles (21 days).

The protocol was approved by the participating sites' ethics boards. Written informed consent was obtained from each patient before enrollment.

Response was evaluated using Response Evaluation Criteria in Solid Tumors 1.0. The primary endpoint was progression-free survival (PFS). Patients receiving at least one dose of study drug were included in PFS or overall survival (OS) analyses.

Blood samples were collected to assess steady-state trough LY293111 plasma concentrations (pre-dose on day 1 of cycles 2 and 3) and peak plasma concentrations of LY293111 and cisplatin pharmacokinetics (postdose day 1 of cycle 2). For biomarker analysis, blood samples were collected before LY293111 dosing (on visit 0 or day 1 of cycle 1, and day 1 of cycle 2). Levels of adipophilin and adiponectin in plasma were monitored to determine whether LY293111 acted as a PPAR-γ agonist. Levels of interleukin-6, interleukin-8, and tumor necrosis factor α were also analyzed. Human plasma samples were analyzed for LY293111 levels by using validated liquid chromatography/electrospray ionization mass spectroscopy/tandem mass spectroscopy methods.

On the basis of label information for gemcitabine in combination with cisplatin,[13] the median PFS for gemcitabine and cisplatin plus placebo was assumed to be approximately 5 months, with a one-sided significance level of 0.2, 75% power, and 33% improvement compared with placebo.

PFS and OS were compared among treatments by using pairwise log-rank tests, and event time distributions were estimated using the Kaplan–Meier method. Tumor response rates were compared among treatments using Pearson's χ^2 test. Adverse events (AEs) were compared among treatments using the Mantel-Haenszel χ^2 test. Changes from baseline in disease-related biomarkers were compared between treatments using the nonparametric Wilcoxon test. Analysis was conducted with SAS version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 203 patients were enrolled in the study; of these, 200 were randomly assigned to study treatment (71 to 200 LY293111 arm, 66 to 600 LY293111 arm, and 63 to placebo arm), and 195 received therapy. Treatment arms were well balanced for prognostic markers (Table 1). The median number of cycles per treatment arm was five; the mean number of cycles was 5.3 for placebo and 4.8 for each of the LY293111 arms.

Efficacy

Median PFS times (95% confidence intervals [CI]) for 200 LY293111, 600 LY293111, and placebo were 4.6

TABLE 1. Demographic and Baseline Characteristics by Treatment Arms

	LY293111 (200 mg BID)+ Gemcitabine+ Cisplatin	LY293111 (600 mg BID)+ Gemcitabine+ Cisplatin	Placebo+ Gemcitabine+ Cisplatin
Patients, total (n = 200)	71	66	63
Patients receiving therapy (n = 195)	70	64	61
Age at entry, yrs			
Median	62.4	60.7	60.9
Range	36.7–81.2	28.5–87.8	27.8–76.6
Origin, n (%)			
White	68 (97)	62 (97)	59 (97)
African descent	0	2 (3)	0
East/Southeast Asian	2 (3)	0	2 (3)
Sex, n (%)			
Female	28 (40)	16 (25)	24 (39)
Male	42 (60)	48 (75)	37 (61)
ECOG PS at entry, n (%)			
0	25 (36)	25 (39)	21 (34)
1	45 (64)	39 (61)	40 (66)
Disease state at entry, n (%)			
IIIB	14 (20)	9 (14)	7 (11)
IV	56 (80)	55 (86)	54 (88)

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

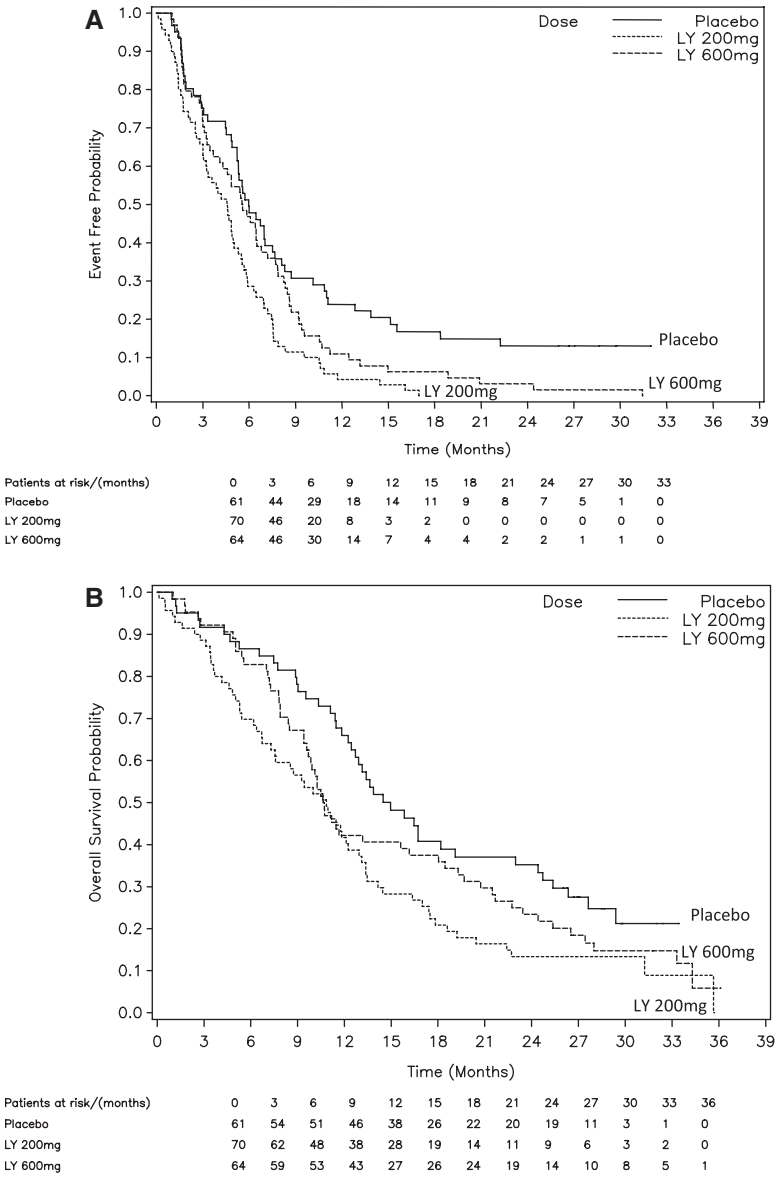

FIGURE 1. Kaplan–Meier estimates for progression-free survival (*A*) and overall survival (*B*) time by treatment group.

(3.2–5.0) months, 5.6 (4.1–6.8) months, and 6.0 (5.2–7.5), respectively (Fig. 1*A*); LY293111 arms were not statistically superior to placebo ($p > 0.20$). Six-month PFS rates (95% CI) were 29% (18%–39%), 47% (35%–59%), and 50% (37%–62%), respectively. Median OS times (95% CI) for 200 LY293111, 600 LY293111, and placebo were 10.8 (7.6–12.9) months, 10.7 (9.7–16.2) months, and 15.0 (12.7–19.1) months, respectively (Fig. 1*B*); the placebo arm had statistically superior survival when compared with the 200 LY293111 arm. The 6-month survival rates (95% CI) for 200 LY293111, 600 LY293111, and placebo were 70% (59%–81%), 83% (74%–92%), and 87% (78%–95%), respectively.

Table 2 summarizes the best tumor response by treatment arms. The difference in overall tumor response among treatment arms was not statistically significant ($p = 0.34$).

Safety

Sixty-three of the 70 patients treated with 200 LY293111 experienced AEs (grade 3, $n = 27$; grade 4, $n = 13$); 62 of the 64 patients treated with 600 LY293111 experienced AEs (grade 3, $n = 19$; grade 4, $n = 6$); and 58 of the 61 patients receiving placebo experienced AEs (grade 3, $n = 23$; grade 4, $n = 8$).

The most common study drug–related AEs were nausea (200 LY293111, 70.0%; 600 LY293111, 70.3%; placebo, 77.0%), vomiting (200 LY293111, 45.7%; 600 LY293111, 56.2%; placebo, 50.8%), and fatigue (200 LY293111, 35.7%; 600 LY293111, 45.3%; placebo, 60.7%). The incidence of diarrhea was higher in 600 LY293111 (78.1%) than in 200 LY293111 (30.0%) or placebo (23.0%). The incidence of the following study drug–related events was statistically significantly different among the treatment arms: fatigue, sensory

TABLE 2. Best Tumor Response by Treatment Arms

Best Response[a]	LY293111 (200 mg BID)+ Gemcitabine+ Cisplatin (*n* = 70)	LY293111 (600 mg BID)+ Gemcitabine+ Cisplatin (*n* = 64)	Placebo+ Gemcitabine+ Cisplatin (*n* = 61)
Complete response, *n* (%)	0 (0.0)	1 (1.6)	1 (1.6)
Partial response, *n* (%)	14 (20.0)	15 (23.4)	18 (29.5)
Overall response, *n* (%)	14 (20.0)	16 (25.0)	19 (31.1)
Stable disease	33	31	23
Progressive disease	15	13	12
Unknown	0	1	3
Unavailable for consideration	8	3	4

BID, twice daily.
[a]For patients with a best response of unknown and not available, insufficient data were available to determine any cycle responses because no follow-up computed tomograms were obtained after baseline.

TABLE 3. Summary of Treatment-Related CTC v2 Grade 3/4 Adverse Events

		LY293111 (200 mg BID)+ Gemcitabine+ Cisplatin (*n* = 70)		LY293111 (600 mg BID)+ Gemcitabine+ Cisplatin (*n* = 64)		Placebo+ Gemcitabine+ Cisplatin (*n* = 61)	
Events	**Grade**	***n***	**%**	***n***	**%**	***n***	**%**
Nausea	3	4	5.7	5	7.8	5	8.2
Vomiting	3	5	7.1	8	12.5	4	6.6
Fatigue	3	3	4.3	2	3.1	7	11.5
Neutropenia	3	16	22.9	9	14.1	13	21.3
	4	9	12.9	4	6.3	5	8.2
Diarrhea	3	3	4.3	8	12.5	1	1.6
Anemia	3	3	4.3	4	6.3	4	6.6
Thrombocytopenia	3	11	15.7	8	12.5	5	8.2
	4	1	1.4	1	1.6	1	1.6
ALT	3	1	1.4	0	0	0	0
AST	4	1	1.4	0	0	0	0
Liver dysfunction	3	1	1.4	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTC v2, Common Terminology Criteria, version 2.

neuropathy, hypomagnesemia, and infection/febrile neutropenia (p <0.05). Table 3 summarizes the treatment-related Common Terminology Criteria grade 3 to 4 AEs.

Of the 195 treated patients, seven on-study deaths occurred, five of which were study-drug related: three because of pulmonary embolism (1 in each arm) and one each because of cardiorespiratory arrest (200 LY263111) and pneumonia (placebo).

Pharmacokinetics

Steady-state pharmacokinetics of LY293111 was achieved by day 1 of cycle 2 in both LY293111 arms. The steady-state level of LY293111 in the 600-dose arm was approximately twice the level observed in the 200-dose arm, but interindividual variability was high. These data suggest that cisplatin and gemcitabine did not have a substantial effect on the pharmacokinetics of LY293111. No effect on the pharmacokinetics of cisplatin was observed for 200 LY293111 plus gemcitabine and cisplatin. The interindividual variability was lower for 200 LY293111 (19.8%) than for placebo (42.1%).

Biomarker Modulation

The median change from baseline in serum adiponectin levels after 7 days of treatment was significantly higher in the 600 LY293111 than in the placebo arm (p <0.05). Adipophilin expression was increased in a dose-dependent but nonstatistically significant manner in LY293111 arms versus placebo (Table 4).

DISCUSSION

Although preclinical studies suggest that LY293111, a PPAR-γ agonist, may exhibit activity against NSCLC cells expressing PPAR-γ, this phase II study demonstrated that low and high doses of LY293111 combined with gemcitabine plus cisplatin did not produce significant improvement in 6-month PFS or OS in patients with NSCLC compared with placebo combined with gemcitabine plus cisplatin. A previous phase II trial in non-pretreated patients with advanced pancreatic carcinoma also failed to show a benefit by combining LY293111 with gemcitabine.[14]

Other efficacy measures were also not significantly affected by treatment with low and high doses of LY293111

TABLE 4. Biomarker Modulation after 1-Week, Lead-In Period of Oral Therapy Only

Biomarker	Change from Baseline[a]	200 mg Twice Daily LY293111 (*N* = 70)	600 mg Twice Daily LY293111 (*N* = 64)	Placebo (*N* = 61)
Adiponection (μg/ml)	*N*	40	48	35
	Median	1.0	1.0	0.0
	IQR	0.0 to 2.0	−0.5 to 2.0	−1.0 to 1.0
	p value, LY vs. placebo	0.053	0.034	NA
Adiophilin (ratio)	*N*	17	24	18
	Median	0.02	0.13	−0.24
	IQR	−0.25 to 0.38	−0.30 to 0.90	−0.45 to 0.15
	p value, LY vs. placebo	0.138	0.166	NA
Interleukin-6 (pg/ml)	*N*	27	28	22
	Median	0.0	1.0	−2.0
	IQR	−6.0 to 3.0	−3.5 to 6.0	−8.0 to 7.0
	p value, LY vs. placebo	0.413	0.199	NA
Interleukin-8 (pg/ml)	*N*	28	19	16
	Median	−2.5	−5.0	−9.5
	IQR	−15.0 to 2.5	−29.0 to 4.0	−22.0 to 10.0
	p value, LY vs. placebo	0.923	0.693	NA
Tumor necrosis factor α	*N*	20	21	12
	Median	0.0	0.0	−0.5
	IQR	0.0 to 1.5	−1.0 to 1.0	−1.5 to 0.0
	p value, LY vs. placebo	0.116	0.434	NA

IQR, interquartile range (25th percentile–75th percentile); *N,* total number of randomized patients in the treatment group; *n* = total number of randomized patients in the treatment group having both baseline and postbaseline measures; NA, not applicable; IL, interleukin; IFN, interferon.

[a]All *p* values used two-sided Wilcoxon *t* approximation.

Other biomarkers (IL-2, IL-4, IL-5, IFN-γ, GM-CSF) not reported if n <10 in at least one treatment arm.

versus placebo. No validated surrogate marker has been identified for the activity of LY293111.[7] An interim analysis of this study with biomarker data was previously presented.[15] This final analysis confirms that, although modulation of serum adiponectin levels and adipohilin expression were observed, treatment efficacy was not affected.

LY293111 did not significantly affect the safety and tolerability of gemcitabine plus cisplatin, except for diarrhea. The mechanism of gastrointestinal activity of LY293111 is not well understood. The phase I study of single-agent LY293111 produced significant gastrointestinal activity, with diarrhea being dose-limiting and the most common toxicity encountered.[12]

Gemcitabine and cisplatin did not seem to have any effect on the pharmacokinetics of LY293111. In addition, LY293111 combined with gemcitabine plus cisplatin did not seem to have a substantial effectS on the pharmacokinetics of cisplatin.

In summary, these results do not suggest any benefit of adding LY293111 to the combination of gemcitabine and cisplatin in patients with advanced NSCLC. Our findings may have implications for other agents as anticancer therapies targeting PPAR-γ that are currently in clinical development.

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